SEX LINKED MICROPHTHALIA SOMETIMES ASSOCIATED WITH MENTAL DEFICIENCY.

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population rising from 415,000 to 657,000, had yielded annual averages for each of the seven-year periods of, respectively, 643 cases and 112 deaths; 1,254 cases and 176 deaths; and 1,137 cases and 146 deaths, reaching, in 1927, 1,826 cases and 219 deaths.

In 1928, when immunization was started, there were 1,632 cases and 157 deaths. Thereafter with each succeeding year's increase in the numbers immunized there has followed a steady decline in the diphtheria incidence and mortality; and as the result of a particularly strenuous campaign in 1933, when over 47,000 children were treated, by the end of 1935 a total of nearly 116,500, or well over 50 per cent. of the child population under 12 years, had been protected. As the accompanying Graph II demonstrates, the fall since 1928 has been remarkable, the records in 1935, with 183 cases and twenty-one deaths, being but a tenth of the figures in 1927, whilst in 1936 only eighteen deaths from diphtheria were recorded in Montreal's population of 863,000. But, to maintain the low incidence and mortality to which diphtheria has fallen in New York and Montreal, the further success of immunization must be dependent on the respective campaigns being continuous and unremitting, in order to keep up a protection rate at least equal to half the number of births each year.

The Position in the British Isles

If such can be achieved in New York and Montreal, why should it be beyond achievement in London and elsewhere in Great Britain? Why should London, with a population three millions less, show six to seven times as many diphtheria cases and deaths as New York? Surely we should not be resigned to a fatalistic view that co-ordination and enterprise of the medical profession, and the necessary education of the general public, cannot overcome apathy and indifference and bring about effective control of diphtheria by means of immunization, directed mainly to the protection of children under 5 years of age. It is encouraging to know that, thanks to Dr. Thomson's efforts, immunization has now become available in Belfast. (Commencing October 1, 1936, he reports that approximately 5,000 have been immunized in the course of the first year's work.)

The accompanying table provides a list of the fifty towns, with their populations, in 1930 and 1936, and the number of diphtheria cases and deaths in that seven-year period, as well as of those immunized up to the end of 1930 and 1935 and during 1936. The figures given under "Immunized" indicate the total of those who have received a complete course of prophylactic inoculation irrespective of post-Schick testing, and do not include either those found Schick-negative on primary test—that is, the naturally immune—or the immunized adults of hospital staffs. In a parallel column is given for each town the approximate "immunized" percentage of the total population.

For comparison similar particulars of three cities in Scotland (Edinburgh, Dundee, and Aberdeen), with Aberdeen County, and three cities in Ireland (Dublin, Belfast, and Cork), have been appended to the list. Of these, Cork, it will be noted, presents the highest protection rate of all—15 per cent.—with about 12,000 immunized in a population of over 80,000 of all ages; and, as the work has largely been devoted to the treatment of children of under 15 years, the proportion of child population protected has reached over 50 per cent. The desired continuance of the fall in diphtheria incidence and mortality recorded in Cork city in 1935 and 1936 will depend on that proportion of the immunized being maintained and increased year by year.

The details of the table attached have been derived either from annual reports of the years concerned or from information kindly supplied, recently as well as in years past, by many medical officers of health, to all of whom grateful acknowledgement is due for their ready help. It remains to point out that the London County Council is in no way responsible for any of the observations made or opinions and conclusions expressed in the course of this paper. I have also to thank Mr. E. S. Glass for his skilful drawing of the graphs.

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Report of the Montreal Department of Health, 1935, pp. 51 and 67.

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SEX-LINKED MICROPHTHALMIA SOMETIMES ASSOCIATED WITH MENTAL DEFICIENCY

copy one

BY

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In 1935 two blind and mentally defective brothers were admitted to Stoke Park Colony. The family history then supplied was strongly suggestive of recessive sex-linked inheritance. This was confirmed when a fuller history was obtained. A search of the literature soon revealed the fact that this particular family had been previously described by Ash (1922). Since 1922, however, several more children have been born, and it also proved possible to extend the pedigree.

It seems desirable, for several reasons, to give some further account of this family. In the first place, although Ash stated that the condition was microphthalmia, he did not describe the appearance of the eyes. Further, he obtained his information from one family, DII 10–18 in the pedigree, and saw only three blind individuals (DII 10, 11, 14), who were then young. Therefore, although it was noted that DII 10 was an epileptic, it was hardly possible for Ash to discover from the persons he saw that the eye defect in this family group was sometimes associated with varying degrees of mental deficiency. As far as I can discover, this is the only certain example of sex-linked microphthalmia that has been described, so on that account, and because of the remarkable variability in the effects of the genetic factor, the family merits a fuller description.

The Inheritance of the Defect

The defect is clearly due to a recessive sex-linked factor, and the pedigree shows no anomaly of any kind. There is no suggestion that any male who receives the factor is not born blind, and certainly none that the heterozygous females are not entirely normal. The defect has appeared in four generations, and there is some evidence that it can be traced for six, for I 7 informed me that her mother often told her that her (the mother's) grandmother certainly had one, and possibly two, blind boys. The six generations would cover a period of about 200 years.

Description of the Eyes

Six blind males from three different families have been personally examined. They are DII 21, 22, DIII 1, DII 10, 11, 14. These are all that could be traced of those still alive, the remaining eight blind males shown in the pedigree being now dead.

DII 21. Aged 17 Years

Both eyes sunken in sockets, cornea normal in diameter. Intraocular tension minus. Nystagmus not observed.

Right Eye.—Cornea shows dense leucoma adherens—no vascularity. Anterior chamber shallow. Pupil drawn up and very small. Lens not seen.

Left Eye.—Opaque cornea (ground-glass appearance) with vessels from ciliary zone. Iris adherent to cornea.

DII 22. Aged 6 Years 7 Months

Both eyes slightly sunken in sockets, cornea normal in diameter. Intraocular pressure minus. Nystagmus.

Right Eye.—Cornea clear, anterior chamber normal, pupil moderately dilated. Iris blackish brown and tremulous. Lens light yellow, soft in appearance, and dislocated downwards and outwards. Fringes of iris pigment adherent to lens.

Left Eye.—Cornea shows leucomata. Newly formed vessels are to be seen running from iris down and out over the lens capsule. Anterior chamber rather shallow. Fully dilated pupil. Lens subluxated forwards—greyish and soft in appearance.

DIII 1. Aged 4 Years 10 Months

Both eyes sunken in sockets. Cornea of normal size and entirely clear. Curvature accentuated, giving deep anterior chamber. Iris bluish grey, with a rather dull, structureless, and homogeneous appearance. Intraocular tension minus. Rapid, rather coarse nystagmus on turning eyes to either side.

Right Eye.—Pupil fixed, about 3 mm. in diameter, with slightly irregular margin. Lens shows streaky white opacities.

Left Eye.—Pupil smaller than in right eye, about 2 mm. in diameter. Lens completely opaque and whitish grey.

DII 10. Aged 29 Years

Both eyes much sunken in sockets. Intraocular tension minus. Nystagmus similar to DIII 1.

Right Eye.—Cornea normal in size; white opaque patches all over. Lens not seen.

Left Eye.—Cornea small; white patches all over. Narrow fringe of iris. Pupil about 8 mm. in diameter, with ragged edge. Lens yellowish white, and soft in appearance.

DII 11. Aged 26 Years

Both eyes much sunken, with everted lower lids. Both corneae small. Intraocular tension minus. Nystagmus similar to DIII 1.

Right Eye.—Cornea shows white patches. Lens not seen.

Left Eye.—Cornea completely opaque; ground-glass appearance. Very similar to left eye of DII 21. Lens not seen.

DII 14. Aged 21 Years

Both eyes somewhat sunken in sockets. Intraocular tension minus. Nystagmus similar to DIII 1.

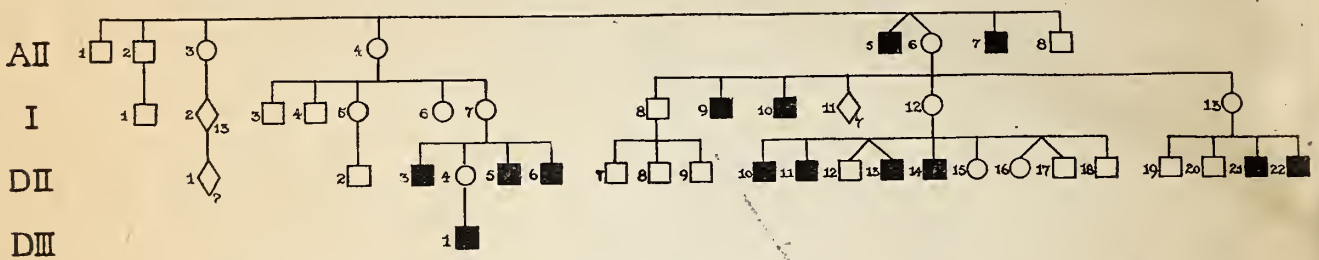
Right Eye.—Cornea normal in size. Dense white patches render it almost completely opaque. Lens not seen.

Left Eye.—Cornea smaller than normal. Opacities, especially a dense central patch, but cornea not as opaque as in right eye. Pupil about 3 mm. in diameter, with slightly irregular margin. Lens opaque and yellowish white.

The mothers of all these boys were seen. All stated that the abnormality could be detected immediately after birth. In the case of the five in which there are corneal opacities both mothers stated definitely that the whitish appearance of the front of the eye was present at birth, and that, as far as they knew, there had been no change in the appearance of the eyes since that time.

The Nature of the Eye Condition

Waardenburg (1932) quotes van Duyse, who, in the French *Encyclopaedia of Teratology* (*Ophthalmological*) divides microphthalmia into three groups. The first is true or simple microphthalmia; the second is microphthalmia associated with coloboma; the third is microphthalmia without coloboma but associated with various other abnormalities, such as opacities of the cornea, aniridia, smallness or absence of the lens, and opacities



Genealogical chart showing the incidence of microphthalmia inherited as a sex-linked recessive condition. (International symbols.)

of the lens. This classification seems to be generally accepted.

The cases here described fall into the third somewhat heterogeneous group. That it should be heterogeneous is perhaps not surprising, for in this family, for example, there are considerable differences not only between affected individuals but also between the eyes of the same individual. Smallness at least of the cornea is itself a feature not always present.

The Mental Condition

Two of the six patients examined may confidently be said to be of normal mentality. These are DII 11 and DIII 1. DII 11, aged 26, is well above average intelligence. The little boy, DIII 1, is only 4 years and 10 months, but he, too, is above the average in mentality for a child of his age. He talks freely and intelligently, and showed much interest in and knowledge of the things around him. He correctly repeated songs and recitations that he had memorized and performed gymnastic exercises that would have been remarkably good for an ordinary boy of his age.

The elder of the two boys at Stoke Park Colony (DII 21) must be classified as an imbecile. He can talk, repeat rhymes, etc., can count his fingers, and is continent, but he needs help in order to dress and to feed himself. He shows little understanding of what is said to him, and his speech includes much meaningless repetition. His brother (DII 22) is an idiot, able to walk but unable to talk or to dress himself. He is incontinent; his activities are purposeless; and he is subject to violent outbursts of temper.

DII 10, aged 29, is an imbecile, though not of as low a grade as DII 21. He walks and talks, but for the most part sits silent. From time to time, however, he is able to express himself coherently when a subject is mentioned that interests him. He can dress and feed but not shave himself. At the age of 7, following an attack of measles, he had epileptic fits which continued till he was 17. After a period of remission lasting four years the fits recommenced and now occur about once a week.

The third surviving blind boy in this family (DII 14) must be classified as feebleminded. He went to the Blind School and learnt to read and copy braille. He copies very slowly, however. His mentality appears to be of about a 10-year level. He is docile and cheerful and can look after himself generally, dressing, washing, and feeding, but not shaving himself. One of his great pleasures is the constant repetition of stories by his elder blind brother about such things as events at the Blind School. Thus of the six males personally examined two are of normal mentality, one is feebleminded, two are imbeciles, and one is an idiot.

It is possible from the very clear information given by their relatives to make some estimate of the mentality of a few of the other affected males who are now dead. The mother of the three boys DII 3, 5, 6 stated that the eldest, who died at the age of 5, could talk and play the piano. So far as she could tell he was quite normal mentally. He died following an epileptic fit, his first. The second boy was an idiot who was unable to talk, or even to walk unassisted. He commenced to have epileptic fits for the first time at the age of 16, and died at the age of 18, following fits. The third boy apparently exhibited the most extreme degree of idiocy in the whole series. He was unable to walk or talk and could not even stand. He was fed by means of a bottle till his death at the age of 14. He did not have any fits. The fourth blind male (DII 13) in family DII 10–18 died at the age of 1 year and 8 months, so no statement can be made regarding his mentality.

As regards the earlier generations the only information available is that AII 5, who died at the age of 47, was mentally defective. This was definitely stated to be so by his nieces.

Notes on Other Persons shown in the Pedigree Chart

AII 3.—The rest of the family have now lost touch with AII 3, but state that she had thirteen children, all normal, and that her daughters have several sons, also all normal.

AII 7.—Died aged 9 years. Blind. Mental state unknown.

Sibship I 8–13.—Birth order and sex of some individuals uncertain, though it seems fairly certain that the total number was 12, including two blind males. Several other children died in infancy before the birth of my informants, I 12 and I 13, who were themselves the youngest in the family. I 9 and I 10 were both blind and died young, before the birth of I 12 and I 13.

DII 16.—Died aged 1 month. Eyes normal.

DII 17.—Died aged 6 months. Eyes normal.

Discussion

Inherited microphthalmia is a rare condition, but in regard to microphthalmia inherited as a sex-linked recessive this family group appears to be the only undoubted case yet described. Waardenburg (1932) in his invaluable book on hereditary diseases of the eye considers it possible that this type of inheritance may have sometimes been overlooked, but quotes Ash's pedigree as the only clear example. I am not aware of any other published since 1932. Apart from this, however, there are several features to be noted. In the first place the appearance of the eyes varies very considerably in different persons, and the two eyes in a single individual may be strikingly different. A somewhat heterogeneous group of maldeveloped eyes has usually been accepted as forming an entity, and there would seem to be at least a genetical justification for this course. Another point is that the appearance of the cornea in some cases could easily be mistaken for the end-result of an ordinary inflammatory process; yet the condition is strictly an inherited one, the cornea is apparently opaque at birth, and there is no suggestion of post-natal inflammation, a point about which I was careful to inquire. The condition therefore would seem to be yet another example of an abiotrophy closely simulating the end-results of an infective process.

Perhaps the most remarkable feature is the association with mental deficiency. The blindness is compatible with normal mentality, as in two of the cases personally examined, but in other instances there may be any grade of mental deficiency, ranging from feeblemindedness to the most extreme idiocy. There is no suggestion of any mental deficiency in the family apart from the blindness. The numerous normal members that I have seen are entirely normal, and would as a group have to be classed as of above average intelligence. Nor could any history be obtained of mental deficiency apart from blindness in those members of the family that I did not see. The persons who provided the information were unusually objective in their statements, and had formed an accurate estimate of the mentality of the blind males; had any persons not blind been mentally defective I am sure that the fact would have been appreciated and that I should have been informed.

It has been noted by several writers that microphthalmia may be associated with mental impairment. For example, Ramsey (1898) states that it is occasionally related to defective mental development, and Parsons (1904) states that there is sometimes an association with brain malformations and idiocy. Kubik (1923) described a 12-day rabbit embryo with complete bilateral anophthalmia and aplasia of the fore-brain and mid-brain. The father of this rabbit had microphthalmia with coloboma. Kubik considers that the condition ranges from the slightest colobomata through microphthalmia, cyclopia, and anophthalmia, to cases in which there is more or less extensive aplasia of the sections of the brain from which the eye is developed. In papers dealing with hereditary microphthalmia in man, however, there is seldom any reference to impaired mental development. Usher (1921) described a family group containing eleven affected persons, and stated that one of these "was mentally affected and died in an asylum"; but such instances would seem to be rare.

In the case of the family described in this paper it is impossible to say, in the absence of the examination of a brain, whether the mental deficiency, when present, is due to specific malformations of the type described by Kubik or whether the entire brain would show the underdevelopment and maldevelopment that is so characteristic of the brains of ordinary mental defectives. The blind and mentally defective persons do not show any abnormal neurological signs of note, and apart from the blindness would fall into the large group of mental defectives of no particular type, so it is perhaps unlikely that the mental impairment is due to cerebral aplasia of a limited and special kind.

The genetic factor in this family group produces very diverse effects and is constant only in producing blindness

of microphthalmic type. It is unprofitable to speculate as to the additional influences that determine such big differences in the mentality of affected persons. They are perhaps unlikely to be genetic, in view of the wide range of the effects and in view of the occurrence of very different mentalities in affected persons in the same sibship. It may be more reasonable to conclude that the organism during critical stages of its development is for genetic reasons abnormally sensitive to non-genetic influences and that these, entirely trivial in the case of normal persons, are on occasion capable of modifying the development of the brain and so of profoundly affecting its ultimate structure.

Summary

1. A family group is described in which microphthalmia is inherited as a sex-linked recessive condition.

2. The appearance of the eyes in six affected persons shows much variation.

3. The blind males may be of normal mentality or may exhibit any grade of mental deficiency from feeble-mindedness to profound idiocy. There is no mental deficiency in the family group apart from the blindness.

I am greatly indebted to Mr. A. E. Iles, consulting ophthalmologist to Stoke Park Colony, for the description given above of the eyes of the two patients at that institution (DII 21, 22) and for his advice on the examination of the other blind persons and on the preparation of this paper.

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MODERN CONTROL OF SCARLET FEVER*

BY

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This paper is written with a view to elucidating some of the problems with which the clinician is confronted when dealing with scarlet fever and haemolytic streptococcal pharyngitis. It is now generally accepted that scarlet fever occurs through certain types of *Streptococcus pyogenes* multiplying in the body and giving off an exotoxin which on gaining admission to the circulation causes the skin capillaries to dilate, the characteristic rash resulting. This toxin is neutralizable by its specific antitoxin.

Whilst working with Dr. F. Griffith some years ago I took thirteen strains of haemolytic streptococci obtained in epidemics of scarlet fever and pharyngitis from different parts of England, and tested their toxigenic power on patients with known skin reactions to standard Dick toxin. We found that the amount of toxin produced by the different strains was very variable, some filtrates giving a positive reaction when 0.1 c.cm. of a 1 in 4,000 solution was injected intradermally, others almost none when 0.1 c.cm. of a 1 in 50 solution was similarly used. When we correlated these findings with the type of epidemic from which the strains had been cultured we found that:

1. In the epidemics caused by the powerful toxigenic strains were many cases of clinical scarlet fever and a few cases of simple pharyngitis.

2. Where medium toxigenic strains were the cause the number of cases of clinical scarlet fever and of pharyngitis were about equal.

3. Where a low toxigenic strain was the cause no clinical scarlet fever cases or only an occasional one appeared among many cases of pharyngitis.

It was clear that erythema, one important element of the clinical syndrome of scarlet fever, may be absent in cases of scarlatinal infection—that is to say, given an acute infection with haemolytic streptococcus a severe or transient erythema may develop or none at all. The conclusion that may be drawn from these observations is that scarlet fever cannot be considered as a specific disease like plague or cholera: it is one of the protean manifestations of streptococcal infection.

Further studies of the immunology of the haemolytic streptococcus show that the exotoxin is only one of its weapons of offence, among others being its lytic and invasive powers. Hence clinically acute pharyngitis caused by a haemolytic streptococcus can occur without resulting rash, if: (1) the patient has sufficient antitoxin to neutralize the toxin produced by the invading streptococcus; (2) the organism has little or no toxigenic power. For these reasons the term scarlet fever, which was introduced before the aetiology of the disease was known, may be misleading. At present tonsillitis with erythema is called scarlet fever, and is a notifiable disease against which the most strict precautions must be taken—for example, hospitalization, isolation, etc.—while pharyngitis caused by the same organism but without erythema is regarded as a mild complaint for which no special measures are necessary. This attitude has caused the clinician much trouble in the past, particularly when dealing with epidemics of scarlet fever or pharyngitis in the wards of children's hospitals or in semi-isolated communities such as schools.

It has been found that the isolation of cases of clinical scarlet fever for six weeks does not stop the spread of the disease. Public health notification and hospitalization have not reduced the morbidity during the past twenty-five years. In several well-known schools outbreaks of scarlet fever have occurred term after term for over a year, often followed by severe complications, although the doctors in charge employed all the usual methods of control laid down in the textbooks. The best example is given by Glover and Griffith (1930), who described an outbreak of "scarlet fever" in a school of fifty boys which continued for three terms. They show how all the cases were caused by the same organism, the fresh outbreaks being brought about by patients whose throats still carried the germ when released after the usual isolation period.

Recently I have had the opportunity of testing clinically the validity of the above experiments and observations in an epidemic which occurred in a Dublin public school.

Table I.—*Showing Time of Occurrence of Eleven Cases of Pharyngitis at a Public School*

June:	1	2	3	4	5	6	7	8	9	10	11
Pharyngitis ..	1		1				1				1
C. Erythema ..		1		1				1			
Carriers						4					

If Table I is examined it will be seen that on June 1 a case of acute pharyngitis occurred. More accurately it

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